REMARKS/ARGUMENTS

Applicants have amended Claims 1 and 76. Applicants respectfully submit that the amendments are formal in nature and do not raise any new issues regarding patentability. Entry of this amendment and favorable reconsideration of all claims are respectfully requested.

Applicants respectfully maintain their traversal of the restriction between claims drawn to monomeric monocyclic peptides and dimeric monocyclic peptides, and the withdrawal from consideration of previously added Claims 88-103.

Rejections under 35 U.S.C. §112 ¶1

"Lack of Enablement"

The Office Action continues to assert that the claims lacked enablement under 35 U.S.C. § 112, ¶ 1. Applicants respectfully traverse.

Starting on page 2, the Office Action states that the Application provides enablement for five aspects related to monomeric monocyclic peptides, but "**does not** reasonably provide enablement for (1) *any* monomeric monocyclic peptides as set forth in [the claims] for treating *any* disease." (bold and italics original). Applicants simply note that treating "any disease" is not a part of the claims and as such cannot be properly used as a basis for rejecting the claims.

The first full paragraph on page 4 of the Office Action discusses the examples of peptides in the specification that have been shown to be ineffective, including both monomeric and dimeric monocyclic peptides. Focusing on these inoperative examples, however, is improper for at least three reasons. First, the law on enablement does not require that all examples are operative. It is well established that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." *See* MPEP § 2164.08(b), and *Altas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577. Second, these inoperative embodiments are in fact excluded from the scope of the claims. Contrary to the assertions in the Office Action, the Claims provide adequate description on the structural characteristics of the claimed monocyclic peptides, and the "inoperative" examples provided the meets and bounds for these structure descriptions. Thirdly, the discussion on the dimeric peptides are irrelevant, because the dimeric claims are not even under consideration.

The remainder of the Office Action appears to focus on the fact that the connector "comprise" is open-ended, and as such expands the scope of the claims. Applicants respectfully submit that the Office misconstrued the claims. The Claims very precisely define the structural aspects of the claimed monocyclic peptides, i.e., a core sequence with two linking groups at either end, and additional sequences that may be added at either end of the core sequence does not affect the core sequence.

Applicants respectfully disagree that the term "is" is open ended, but in the interest of expediting prosecution, have amended Claim 1 to replace "is" with "consists of," obviating any concerns the Examiner may have in this regard.

The first full paragraph on page 7 of the Office Action asserts that a cyclic peptide comprising the various SEQ ID NOs may or may not maintain the structural or functional characteristics of the SEQ ID NOs themselves, and that the specification provides insufficient guidance and working examples. Applicants respectfully disagree. Again, as stated above, the possible presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The test is "whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." *See* MPEP § 2164.08(b), and *Altas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577. The instant application, with the detailed and numerous examples, provide ample guidance as to how one can arrive at and test the monomeric or dimeric monocyclic peptides for the presence of desired functions. *In any event*, those peptides that do not have the desired function are outside the scope of the claims, as the receptor binding loops do not "mimic a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D" (see Claim 1).

The Office Action repetitively asserts that "without the specific amino acid residues or SEQ ID NO, there is no structure associated with the phrase 'monomeric monocyclic peptide." Applicants respectfully disagree, and submit that the state of the art in polypeptide chemistry is such that a peptide can be defined in ways other than its primary structure, such as by its tertiary structure attributes and a core sequence, coupled with a functional limitation. In fact, this is probably more meaningful that just a string of amino acids alone without any insight into the structure or function of the polypeptide sequence.

Furthermore, as previously elaborated, only routine experimentation is required to arrive at the claimed monocyclic peptides, and to test whether they have the requisite biological activities, and that the specification provides a reasonable amount of guidance. Contrary to the assertions in the Office Action, the claimed monocyclic peptides do not encompass an infinite number of peptides. Rather, all of the claimed peptides, as demonstrated by the working examples, are based on the loop fragments of the growth factors VEGF, VEGF-C or VEGF-D. Because the loops are known to have only a small number of residues, only a very limited amount of screening would be required to identify those that, when cyclized, maintain their affinity with one of the receptors for the growth factors. This amount of experimentation is not "undue" in the context of enablement analysis under 35 U.S.C. § 112, 1.

"Lack of Written Description"

The Office Action maintained the rejection of all pending claims for alleged lack of written description under 35 U.S.C. § 112, first paragraph. The Office Action states that the specification contains only three examples, i.e. SEQ ID NOs: 5, 6 and 7, that have actually been shown to have the claimed biological functions, and thus does not provide an adequate written description of the claimed genus. Applicants respectfully traverse.

Applicants respectfully submit this rejection is improper because the specification describes the subject matter as claimed in such a way as to reasonably convey to one ordinarily skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus of monocyclic peptides and dimers thereof, and the specification describes numerous representatives of this genus, e.g. Peptides 1, 2 and 3 (corresponding to SEQ ID NOs: 5, 6, and 7) (mononers) and Peptides 4, 5 and 6 (dimers). In addition, the specification describes how variants of the specifically disclosed core sequences can be obtained by an ordinarily skilled person, and further provides guidelines as to which specific amino acid residue of the polypeptide are conserved for maintaining a receptor binding activity. See e.g. page 15, lines 30 et seq. of the specification. Furthermore, methods for testing such variants for receptor-binding activity are specifically described, see e.g. Example 4.

As discussed above, the open-ended connector "comprising" in the claims does not make the claims less described, because, although it is theoretically possible to add an infinite number of additional amino acid to the precisely defined core sequence, structural and further functional limitations of the claims dramatically limit the possibilities.

To the extent the Examiner considers the term "is" is open-ended, Claim 1 has been amended and replaced with "consists of," to remove this concern.

As the claimed peptides do not have to be more effective than those possessing the native loop sequence as the core sequence, and the claimed genus is not highly variable in view of the fact that the loop sequences are relatively short, are well-characterized, and have highly conserved structural and functional characteristics. Accordingly, applicants respectfully submit that the specification has described sufficient members of the genus, and an ordinarily skilled person would consider that applicants had possession of the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

New Matter

The Office Action rejected various pending claims, asserting that they contain phrases that "represent a departure from" the original specification and claims. Applicants respectfully traverse.

The Office Action asserts that the specification, while discloses a monomeric monocyclic peptide inhibitor based on loops 1, 2 or 3 VEGF-D, does not provide support for "a receptor binding loop 1, 2 or 3 of VEGF, VEGF-C." Applicants respectfully disagree.

As an initial matter, Example 1 of the Specification makes apparent that the 3-D structure of VEGF is known, and from this 3-D structure the loops of VEGF are apparent by visual inspection. It is well-known that all members of the VEGF family of cisteine knot proteins have loops 1, 2 and 3. Using the "homology modeling" technique (see Example 1), the specifics on the loops of VEGF-D were derived based on known 3-D structure of VEGF. Because the sequence of VEGF-C is also known, the specification also taught that the loops for VEGF-C are derived in a similar fashion. For example, at Page 3, lines 32 et seq., the Specification states that "[e]ach VEGF family member has between 30% and 45% amino acid sequence identity with VEGF. The VEGF family members share a VEGF homology domain which contains the six cysteine residues which form the cystine-knot motif." Furthermore, on page 12, lines 18 et seq., it is specifically stated that "each monomer of the VEGF dimer resembles other cystine-knot proteins, having an elongated structure consisting of pairs of twisted, anti-parallel ß-strands connected by a series of solvent-exposed loops." Furthermore, page 13, lines 21-22 of the specification teaches that the inventive monocyclic peptides are "*based on* the peptide sequences

of exposed loops of growth factor proteins, *such as* loops 1, 2 and 3 of VEGF-D." (emphasis added).

Therefore, applicants respectfully submit that the phrase "a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C or VEGF-D" is a mere re-phrasing of "a receptor-binding loop based on the receptor-binding loop 1, 2 or 3 of VEGF-D," and is more clear and distinct. Because it is well-established that "mere rephrasing of a passage does not constitute new mater (see MPEP § 2163.07, II, citing In re Anderson, 471 F.2d 1237 (CCPA, 1973)), applicants respectfully submit the use of the new phrase is permissible and respectfully request its rejection under 35 U.S.C. § 112, ¶ 1.

Similarly, applicants respectfully submit that the phrase "first linking group at one end of the core sequence and second linking group at the other end of the core sequence" is mere re-wording, for clarity purpose, of the description of the same meaning in the Specification (*see. e.g.* fifth to line on page 17 and line 9, page 19. *See also* Original claims 19 and 33: "cyclizing peptide loop fragments of said growth factor protein or corresponding loop fragments").

Finally, applicants submit that the same meaning of the phrase "deleting at least one amino acid from said loop prior to cyclizing the peptide" is conveyed at, *inter alia*, original Claim 9 ("deleting one or two internal amino acid residues from said loop fragment prior to cyclizing the peptide").

Accordingly, applicants respectfully submit that the Office Action's new matter rejections are improper and should be withdrawn.

Rejections under 35 U.S.C. § 112, ¶ 2

The Office Action finally rejected Claims 76-79 for indefiniteness under 35 U.S.C. § 112, ¶ 2, stating that the phrase "C-terminal carboxyl acid function" in Claim 76 is ambiguous and indefinite. In order to expedite prosecution, applicants have amended Claim 76, replacing this phrase with "C-terminal carboxyl" to correspond with the "N-terminal amine" group with which a constraint is formed. Accordingly, applicants respectfully submit that this rejection has been overcome.

Conclusion

Applicants respectfully submit that all claims are now in condition for allowance and solicit an early indication from the Examiner to this effect. If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (CAM #: 029065.48505US).

Respectfully submitted,

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